Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	10/507,466	OSTERMEIER, MARC	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 08 May 2009 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).

5. ☒ Applicant's reply has overcome the following rejection(s): See Continuation Sheet.

6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *None*.
   Claim(s) objected to: *None*.
   Claim(s) rejected: *1-5,7,8,14 and 45-47*.
   Claim(s) withdrawn from consideration: *None*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).

9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).

10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.

12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____

13. ☐ Other: _____.

/Shin-Lin Chen/
Primary Examiner, Art Unit 1632

Continuation of 5. Applicant's reply has overcome the following rejection(s): 35 U.S.C. 112, first paragraph, new matter rejection of claims 45-47.

Continuation of 11. does NOT place the application in condition for allowance because: Applicant argues that the claims have been amended to recite inserting randomly an insertion nucleic acid into an acceptor nucleic acid carried out by a method selected from nuclease treatment … (amendmnet, p. 6). This is not found persuasvie because of the reasons of record. The specification fails to provide adequate guidance and evidence for how to treat a nucleic acid with nuclease, mechanical shearing, chemicals or radiation for the claimed method in vivo, how to prepare randomly linearized insertion sequence and acceptor sequences with nuclease, mechanical shearing, chemicals or radiation in a cell in vivo and how to perform random insertion of an insertion sequence into an acceptor sequence in vivo. The claims encompass any target cell at numerous different locations in a subject. There are various barriers before a outside agent can reach its target cells, for example, skin cells, muscle cells, layers of dermal cells, blood vessel wall cell membranes, nucleases, proteases and lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids. There is no evidence of record that demonstrates treating a nucleic acid, including insertion sequence and acceptor sequence, with nuclease, mechanical shearing, chemicals or radiation in vivo, and performing random insertion of an insertion sequence into an acceptor sequence in vivo. Lacatena reference does not teach or suggest assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, and the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state, such as an activity. Applicant further argues that page 17 line 29 of the specification teaches "a change in state in either the insertion sequence or acceptor sequence will result in a change in state of respective other portion of the fusion" and the term "coupled" refers to a state which is dependent on another state such that a measurable change in the other state is observed. Applicant cites Figures 3A-3G and lists different examples of insertion polypeptide and acceptor polypeptide (amendment, p. 7-12). This is not found persuasive because of the reasons of record. Generation of the hubeta2AR-phoA fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. PhoA can be considered as an insertion sequence and the hubeta2AR (human beta2-adrenergic receptor) protein can be considered as an acceptor sequence. PhoA encodes bacterial alkaline phosphatase and hubeta2AR encodes human beta2-adrenergic receptor. The state of PhoA and the state of hubeta2AR are separate before fusion and a new state is formed when both PhoA and hubeta2AR are fused together. The state of alkaline phosphatase is coupled to the state of the human beta2-adrenergic receptor and the fusion protein comprises a state. Lacatena teaches assaying the alkaline phosphatase activity of the fusion protein. A fusion protein can respond to a stimulant or inhibitor, therefore, any fusion protein is a modulatable molecule. Further, a change in the state of bacterial alkaline phosphatase, e.g. a change in protein sequence, can change the state of hubeta2-adrenergic receptor in the fusion protein because a change in protein sequence can resut in a conformational change and possibley biological function in the fusion protein. Thus, Lacatena does teach every element of the claims. Applicant argues that Anderson reference does not teach each comprise a state such that the state of one is coupled to the state of another such that a measurable change in the other state is observed. Anderson does not teach assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, and the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state. The state of the polypeptide encoded by the acceptor nucleic acid is coupled to the state of the polypeptide encoded by the insertion nucleic acid and vice versa (amendment, p. 12-13). This is not found persuasive because of the reasons of record. Anderson teaches fusing random peptide into GFP to generate GFP fusion protein via insertion of nucleic acid. The random peptide is fused to an internal position of the GFP and the peptide can be inserted at virtually any position but preferred positions include insertion at the very tips of loops on the surface of the GFP (e.g. column 17, lines 1-38). Generation of the GFP fusion protein constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. The peptide can be considered as an insertion sequence and the GFP can be considered as an acceptor sequence, which can have a deletion, a substitution or insertion. The state of the random peptide and the state of GFP are separate before fusion and a new state is formed when both the random peptide and GFP are fused together. The state of the new sate is dependent on the state of random peptide and the state of GFP. The inducible promoter, such as Tet regulatory element, is responsive to inducer, such as tetracycline. When inducer, such as tetracycline, is present, the fusion molecule (fusion nucleic acid operably linked to the inducible promoter) switches state in response to the signal (the inducer, such as tetracycline), which is a measurable change. Further, a fusion protein can respond to a stimulant or inhibitor, therefore, any fusion protein is a modulatable molecule. A change in the state of random peptide, e.g. a change in protein sequence, can change the state of GFP in the fusion protien because a change in protien sequence can result in a conformational change and possiblely biological function in the fusion protein. Thus, Anderson teaches every element of the claims. Applicant argues that the Manoil reference does not teach assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, and the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state (amendment, p. 13-14). This is not found persuasive because of the reasons of record. The insertion of TnphoA into a gene (transposon insertion) is random and the fusion gene encoding hybrid proteins with alkaline phosphatase activity are detected as blue colonies on media containing the alkaline phosphatase indicator dye (e.g. p. 515, right column). Generation of the hybrid proteins constitutes insertion of an insertion sequence into an acceptor sequence and said insertion couples the state of the insertion sequence to the state of the acceptor sequence. The resulting hybrid protein or gene encoding said hybrid protein is a new state. A fusion protein can respond to a stimulant or inhibitor, therefore, any fusion protein is a modulatable molecule. A change in the state of hybrid protein component, e.g. a change in protein sequence, can change the state of another hybrid protein component in the fusion protien because a change in protien sequence can result in a conformational change and possiblely biological function in the fusion protein. Thus, Manoil teaches every element of the claims. Applicant argues that the Mountford reference does not teach assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, and the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state (amendment, p. 14-15). This is not found persuasive because of the reasons of record and the reasons set forth above. Mountford teaches gene trapping for identifying developmentally regulated genes based on the random integration of a reporter into chromosomal transcription units. Mountford further teaches that IRES-containing gene trap construct pGT1.8Iresbetageo enhances frequency of productive integration as compared to control vector (e.g. p. 182, right column). The gene trap vector is an insertion sequence and the choromosomal transcription units are

acceptor sequences. The gene trap vector encodes betagal protein and the chromosomal transcription unit encodes another protein. The resulting fusion molecule is a new state. A fusion protein can respond to a stimulant or inhibitor, therefore, any fusion protein is a modulatable molecule. Applicant argues that the Ong reference does not teach assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, and the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state (amendment, p. 15). This is not found persuasive because of the reasons of record and the reasons set forth above. Ong teaches preparation of gene trap DNA construct comprising a mutagenic, detectable component containing a IRES linked to a reporter gene and a functional unit comprising a reporter gene under the control of PGK promoter. Transfection of the gene trap construct via electroporation into ES cells results in random integration into ES cell genome by illegitimate recombination. The gene trap DNA construct is an insertion sequence and the ES cell genome is acceptor sequence. The gene trap DNA encodes a reporter and the trapped gene in ES cell genome encodes another protein. The resulting fusion molecule is a new state. A fusion protein can respond to a stimulant or inhibitor, therefore, any fusion protein is a modulatable molecule. Applicant argues that Anderson or Norris reference does not assembling a modulatable molecule comprising inserting randomly an insertion nucleic acid sequence into an acceptor nucleic acid sequence, and the insertion nucleic acid sequence and the acceptor nucleic acid sequence each encode a polypeptide that comprises a state (amendment, p. **16**). This is not found persuasive because of the reasons of record and the reasons set forth above.